

Tsutsumi reference”). Applicant respectfully traverses the rejection because the Tsutsumi reference fails to disclose every limitation of the amended claims.

“A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); M.P.E.P. § 2131. During examination, when not defined in the specification, the words of a claim must be accorded their plain meaning. M.P.E.P. § 211.01. In other words, they must be read as they would be interpreted by those of ordinary skill in the art. M.P.E.P. § 211.01; *In re Sneed*, 710 F.2d 1544 (Fed. Cir. 1983).

Preliminarily, Applicant notes that claims 1 and 14 have been amended to recite “PEG molecules having an approximate weight average molecular weight in the range of 10,000 to about 40,000” rather than “in the range of **about** 10,000 to about 40,000.” (emphasis added). Support for the amendments is found in the specification at, for example, page 4, lines 21 to 26.

Applicant respectfully submits that the Tsutsumi reference fails to disclose or suggest every limitation of the amended claims when the claims are read as they would be interpreted by those of ordinary skill in the art. The Tsutsumi reference describes TNF modified with PEG of a weight average molecular weight of 5,000 (See page 9). Claim 1 as amended recites TNF covalently bound to PEG having an approximate weight average molecular weight in the range of 10,000 to about 40,000, and claim 2 recites TNF covalently bound to PEG having an approximate weight average molecular weight in the range of about 20,000 to about 30,000. The Office Action asserts that a molecular weight of 5,000 is an approximate weight average molecular weight in the range of about 10,000 to about 40,000 and is an

approximate weight average molecular weight in the range of about 20,000 to about 30,000. (Office Action dated April 8, 2002, page 4, lines 7 to 10). Applicant respectfully disagrees. Because the claim term “about” is not defined in the specification, it must be accorded its plain meaning, or the meaning that would be ascribed to the term by those of ordinary skill in the art. The Merriam-Webster dictionary defines the word “about” to mean “reasonably close to.” (See Merriam-Webster’s Collegiate Dictionary, 10th Edition, Merriam-Webster, Inc., Springfield, MA, page 3.) Applicant respectfully submits that those of ordinary skill in the art would not consider a weight average molecular weight of 5000 to be reasonably close to a weight average molecular weight of 10,000 to 40,000. Nor would those of ordinary skill in the art consider a weight average molecular weight of 5000 to be reasonably close to a weight average molecular weight of 20,000 to 30,000. Nevertheless, to advance prosecution by further clarifying the claimed subject matter, claims 1 and 14 have been amended to delete “about” before 10,000 and to recite, *inter alia*, TNF covalently bound to PEG having an approximate weight average molecular weight in the range of 10,000 to about 40,000.

Applicants respectfully submit that the Tsutsumi reference, therefore, fails to disclose or suggest a modified TNF bound to PEG having an approximate weight average molecular weight in the range of 10,000 to about 40,000 or having an approximate weight average molecular weight in the range of about 20,000 to about 30,000. Applicant respectfully submits that the Tsutsumi reference thus fails to disclose or suggest every limitation of the present claims when the words of the claims are accorded their plain meaning.

Although the Office Action asserts that “[t]here is nothing in the specification or the prior art to provide any indication as to what range of molecular weight is covered by or excluded from the terms “about”, “bordering on the ridiculous”, or “reasonably close to,”

(Office Action issued November 4, 2002), as discussed above, during examination, the words of the claims must be accorded the meaning that would be given to them by those of ordinary skill in the art. Thus, the molecular weights covered by the terms “about 10,000 to about 40,000” and “about 20,000 to about 30,000” are the molecular weights that those of ordinary skill in the art would consider to be reasonably close to the recited molecular weight ranges. As previously discussed, Applicant respectfully submits that those of ordinary skill in the art would not consider a weight average molecular weight of 5,000 to be reasonably close to a weight average molecular weight of 20,000 to 30,000. Applicant accordingly, respectfully, requests withdrawal of the rejection.

## **II. Alleged Obviousness**

Claims 1 and 8 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over the Tsutumi reference in view of Nakamura, S., *et al.*, *Int. J. Cancer* 48:744-748 (1991) (hereinafter “the Nakamura reference”). Applicant respectfully traverses the rejection because the combined teaching of the cited references fails to teach or suggest every limitation of the claims.

To establish *prima facie* obviousness, the PTO must satisfy three requirements. First, the Patent Office must provide objective evidence that the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, contains some suggestion or incentive that would have motivated those of ordinary skill in the art to modify a reference or to combine references. *In re Lee*, 61 U.S.P.Q.2d 1430, 1433 (Fed. Cir. 2002); *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1998). Second, the proposed modification or combination of the prior art must have had a reasonable expectation

of success, determined from the vantage point of those of ordinary skill in the art, at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Finally, the prior art reference or combination of references must teach or suggest all the limitations of the claims. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970).

Assuming *arguendo* that those of ordinary skill in the art would have been motivated to combine the teachings of the Tsutsumi reference with those of the Nakamura reference, which Applicant does not concede, the combination does not teach or suggest all the limitations of the present claims. Claim 1 as amended recites modified TNF comprising TNF covalently bound to between about five and twelve PEG molecules having an approximate weight average molecular weight in the range of 10,000 to about 40,000. Claim 8 recites the modified TNF of claim 1 wherein the TNF is human TNF mutated by deleting amino acids 1-9 of the mature TNF protein. The Tsutsumi and Nakamura references, when considered alone or in combination, fail to teach or suggest the modified TNF of claims 1 and 8.

As previously discussed, the Tsutsumi reference describes TNF modified with PEG of a weight average molecular weight of 5,000, and fails to teach or suggest TNF covalently bound to PEG having an approximate weight average molecular weight in the range of 10,000 to about 40,000, as recited in amended claim 1. The Nakamura reference fails to teach or suggest TNF covalently bound to PEG, much less TNF covalently bound to PEG having an approximate weight average molecular weight in the range of 10,000 to about 40,000.

In addition, the Tsutsumi and Nakamura references each also fail to teach or suggest human TNF modified by deleting the first nine amino acids of the mature polypeptide, as

recited in claim 8. The Tsutsumi reference describes the full-length, mature TNF polypeptide. The Nakamura reference describes a TNF- $\alpha$  mutant in which the 7 amino-terminal amino acids are deleted and the eighth, ninth, and tenth amino acids are substituted.

Although the Office Action asserts that “Nakamura’s TNF wherein amino acid residues 1-7 are deleted and amino acid residues 8-10 are substituted is TNF mutated by deleting amino acids 1-9 of the mature TNF protein,” (Office Action issued November 4, 2002, page 4), Applicants respectfully submit that the polypeptide described in the Nakamura reference is *not* TNF produced by deleting the first nine amino acids of human mature TNF. The second sequence of the Sequence Listing (SEQ ID NO:2) depicts the amino acid sequence of human mature TNF. As can be seen, the polypeptide is 233 amino acids in length. When amino acids 1 to 9 of this polypeptide are deleted, a polypeptide of **224** amino acids is produced. In contrast, when the seven amino-terminal amino acids of human mature TNF are deleted, and amino acids 8 to 10 are substituted, as described in the Nakamura reference, a polypeptide of **226** amino acids is produced. Accordingly, the polypeptide described in the Nakamura reference is not the polypeptide produced by deleting the first nine amino acids of human mature TNF, and the Nakamura reference fails to teach, disclose, or suggest such a polypeptide.

Accordingly, a combination of the Tsutsumi and Nakamura references not only fails to teach, disclose, or suggest TNF covalently bound to PEG having an approximate weight average molecular weight in the range of 10,000 to about 40,000, but also fails to teach, disclose, or suggest modified human TNF mutated by deleting amino acids 1 to 9 of the mature TNF protein. The combined teaching of the Tsutsumi and Nakamura references, therefore, fails to teach or suggest all the limitations of the present claims. Applicant

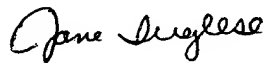
accordingly, respectfully submits that the Office Action has failed to establish *prima facie* obviousness, and requests withdrawal of the rejection.

**Conclusion**

Applicant believes that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable Action is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,



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Date: February 3, 2003

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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**In the Claims**

Claims 1 and 14 have been amended as follows.

1. Modified TNF, comprising TNF covalently bound to between about five and twelve PEG molecules having an approximate weight average molecular weight in the range of [about] 10,000 to about 40,000.

14. A method of enhancing the circulating half life of TNF while reducing its toxicity comprising modifying said TNF by covalently bonding to it between about five and twelve PEG molecules having an approximate weight average molecular weight in the range of [about] 10,000 to about 40,000.

Claims 9 to 13 and 18 to 23 have been cancelled.